UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,973	02/26/2002	James S. Norris	14017-004002 /PSU 96-1566	8113

26161 7590 10/17/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,973	NORRIS ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Other than US Patent No. 6,271,359, all the remaining references cited in this action were previously forwarded to Applicants during the prosecution of parent application 09/338,942.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-24, and 26-38 are rejected under the judicially created doctrine of double patenting over claims 1-5 of U. S. Patent No. 5,824,519.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-24 and 26-38 are generic to all that is recited in claims 1-5 of U.S. Patent No. 5,824,519. That is, claims 1-5 of U.S. Patent No.

5,824,519 fall entirely within the scope of claims 1-24 and 26-38 or, in other words, claims 1-24 and 26-38 are anticipated by claims 1-5 of U.S. Patent No. 5,824,519. The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Recombinant nucleic acids comprising a tissue-specific promoter upstream from a sequence encoding a 5'-autocatalytically cleaving ribozyme, a trans-acting ribozyme that binds and cleaves a selected RNA molecule.

4. Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No.6271359. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the issued Patent recite recombinant nucleic acid comprising a nucleotide sequence encoding an autocatalytically cleaving ribozyme and one or more trans-acting ribozyme(s), operably linked to a tissue-specific or pathogen-specific promoter; recombinant nucleic acid comprising one or more ribozyme cassettes, wherein said ribozyme cassettes include pClip, pChop, and pSnip; vectors comprising said recombinant nucleic acid sequences; and virions comprising said recombinant nucleic acid, wherein said virions include a bacteriophage, and further wherein said bacteriophages include P1 and lambda phage bacteriophages. Claims 1-16 of the instant application are obvious variants of claims 1-2, 11-16, and 21-22 of US Patent No. 6271359.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 28, 30, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 28, 30 and 32 recite "the liposome of claim 5 or 6". There is insufficient antecedent basis for this limitation in claims 5 and 6.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 27-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 27-32 read on methods of treating an infection in a subject comprising administering to a subject compositions or virions comprising a nucleotide sequence encoding an autocatalytically cleaving ribozyme and one or more trans-acting ribozymes operably linked to a tissue-specific or pathogen-specific promoter.

The specification as filed provides several *in vitro* examples wherein ribozyme constructs were used to reduce the level of expression of a particular gene in a cultured cell system. The method of use referred to in claims 27-32 imply *in vivo* applicability for enablement purposes.

However, the specification as filed does not provide sufficient guidance and/or instruction that would allow one of skill in the art to use the claimed invention throughout the full scope of the claims.

It is well established in the art that there is a significant level of unpredictability regarding the behavior of nucleic acid base therapeutics. According to Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of oligonucleotide based therapeutics are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes several "non-antisense effects", for example phosphorothioate modified oligonucleotides tend to bind to many proteins, protein binding in general by oligonucleotides may influence cell uptake, distribution, metabolism and excretion. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense or ribozyme based compounds unpredictable, and thus much experimentation is required to screen multiple antisense compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism."
In addition, Branch teaches that the successful delivery of antisense/ribozymes to their specified target *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Antisense based therapy is a highly unpredictable and field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, the specification as filed does not describe the use of liposomes or virions comprising the ribozyme constructs of the instant invention for the treating an infection or a tissue-specific disease or condition, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery and behavior of ribozymes *in vivo* and further with the production of secondary effects such as alleviating killing or weakening an infection in a patient or ameliorating diseased tissue in a subject, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining the target gene associated with the pathogenesis of an infection and/or a tissue-specific disease, determining the structure of the trans-activating ribozyme used to cleave

the mRNA associated with said target gene and determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of a gene) is obtained. The specification as filed provide sufficient guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1-3, 6-7, 10-11, and 17-18 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Norris et al. (US 5,824,519A).

Norris et al. teach recombinant nucleic acids comprising a tissue-specific promoter upstream from a sequence encoding a 5'-autocatalytically cleaving ribozyme, a trans-acting ribozyme that binds and cleaves a selected RNA molecule. Norris et al. provides an example wherein the ribosomal RNA polymerase I(A) tissue-specific promoter binding sites is used in their ribozyme producing constructs (col. 5, lines 55-62). One particular example of the ribozyme constructs includes the pClip ribozyme cassette, which comprises a tissue specific promoter-binding site upstream from a sequence encoding a 5' autocatalytically cleaving ribozyme sequence, a catalytic ribozyme comprising a target RNA-specific binding site and a 3' autocatalytically cleaving ribozyme sequence (Figure 3, and col. 3, lines 28-32). Norris et al.

also provide methods describing the delivery of the ribozyme constructs into cells by administering liposomes comprising said ribozyme constructs to said cells (col. 7, lines 62-67).

Norris et al. teach each and every aspect of the instant invention thereby anticipating applicant's claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 1-26, and 33-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Norris et al. (WO98/24,925).

Norris et al. teach nucleic acid molecules comprising tissue-specific and pathogen-specific promoters positioned upstream from a sequence from a sequence encoding ribozymes comprising a 5' autocatalytically cleaving ribozyme sequence, a catalytic ribozyme comprising a target RNA-specific binding site and a 3' autocatalytically cleaving ribozyme sequence. The Norris et al. reference further teaches wherein said catalytic ribozymes target rpoA, secA, ftsZ and dnaG RNA transcripts. This reference further teaches vectors comprising said nucleic acid molecules and those comprising multiple ribozyme structures, virions comprising said nucleic acid molecules, liposomes comprising said nculeic acid sequence, and methods for both treating and delivering said nucleic acid into cells. A specific example of a ribozyme construct disclosed by Applicants includes a construct against the *secA* gene inserted into the pClip vector (P. 44).

Norris et al. teach each and every aspect of the instant invention thereby anticipating applicant's claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-24, and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. or Ruiz et al. in view of Ohta et al.

Taira et al. provide a recombinant plasmid containing a sequence encoding any genes inserted between 5' and 3' self-cleavage ribozymes. The recombinant plasmid can be amplified in vivo as well as in vitro while growing the host cell. When obtaining RNA transcripts of the inserted sequence, the recombinant plasmid does not require a restriction enzyme digestion step (run-off transcription) since cis-acting ribozymes perform self-catalyzed cleavage at 5' and 3' sides of the inserted sequence once it is transcribed. In this specific example, the trans-acting RNA enzyme sequence is inserted between 5' and 3' cleavage ribozymes. However, the trans-acting ribozyme sequence in the recombinant plasmid can be replaceable with any other sequence (e.g., antisense RNA, RNAs of HIV-1, HDV and other RNA viruses etc.). This construct is especially useful since each unit, consisting of 5' processing ribozyme, inserted sequence, and 3' processing ribozyme, can be connected in tandem. By so doing, ribozymes targeted to various sites can initially be transcribed as a long RNA chain which subsequently undergoes cleavage to produce independent trans-acting ribozymes, each possessing a specific target site.

However, neither Taira et al. nor Ruiz et al. expressly disclose the use of tissue-specific or pathogenic specific promoters in their recombinant plasmids.

Ohta et al. discloses the use of tissue-specific promoters in recombinant plasmids encoding trans-activating ribozymes targeting the H-ras RNA transcript. Ohta teaches that the use of tissue-specific promoters in their ribozyme constructs allows directed expression of ribozymes and provides a rational strategy for the treatment of human cancers.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to design recombinant nucleic acid sequences comprising a nucleotide sequence encoding self-cleaving ribozymes and one or more trans-acting ribozymes operably linked to a tissue-specific or pathogen-specific promoter since the tissue specific or pathogenic specific promoter would allow for directed expression of their ribozyme constructs to only tissues where the ribozyme is required to function.

One having ordinary skill in the art would have been motivated to do this because directed expression of ribozyme constructs in only tissues where the construct is need would increase the efficacy of ribozyme therapeutics.

Furthermore, neither the Taira et al. reference nor the Ohta et al. reference teaches the use of all the various tissue-specific and pathogenic-specific promoters recited in claims 37-38 of the instant application. However, the Ohta et al. reference does teach the use of tissue-specific promoters, and furthermore it would have been obvious to substitute one equivalent promoter for another.

Therefore the invention as a whole is *prima facie* obvious over Taira et al. in view of Ohta et al.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE